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Geometrically Optimized 3D Printed Mini-Devices for Oral Drug Delivery

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INTRODUCTION & AIM

Within the research on the development of protective carrier platforms intended for oral drug delivery, polymeric microcontainers with sizes around 300 micron have been proposed as a novel system with a unidirectional drug release (1, 2). So far, microcontainers have been fabricated with simple cylindrical shapes in high-throughput fabrication methods such as photolithography or hot-embossing (3, 4). This work investigates the influence of microcontainer-geometry on its overall performance as a drug carrier system. Therefore, various container geometries are designed and rapidly fabricated by employing a micro-additive manufacturing technique. The effect of different geometries on carrier-performance related characteristics, such as mucoadhesion and adhesion-orientation (illustrated in Fig.1) shall be assayed.

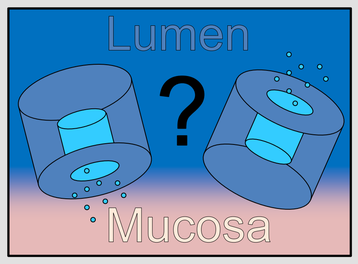

Fig.1 Microcontainer adhesion-orientation problem.
One fundamental question underlying the project is how to design the microcontainer geometry in order to promote adhesion in one particular direction.

Overall, the presented project can be divided into three different categories:

Design → Fabrication → Characterization

METHODS

Design

We assume that a strong contrast between top and bottom geometry of the microcontainers will lead to a favored adhesion-orientation in one particular direction. Furthermore, we assume that a favored adhesion-orientation with the reservoir side of the microcontainers facing the mucosa will lead to an increased uptake of drug. A MATLAB code for solving heat conduction problems was employed to generate "hairy" designs (5). Using different settings, two topology optimized microcontainer-designs were created: TO1-big and TO2-complex (Fig. 2). Other additional simple designs, including a bio-inspired "phage-like" design, were manually created using OpenSCAD and Solidworks software (Fig. 2).

Fig.2 STL mesh-file renderings of the chosen microcontainer designs.

One further idea underlying these designs is that the attachment of microstructures could facilitate the interaction between the ultrastructural space (mucus, intestinal villi/microvilli) of the intestinal wall and the microcontainers to promote bioadhesion.

Fabrication

The STL design-files were printed using an EnvisionTec Micro Plus Hi-Res DLP (Digital Light Processing) µSLA-3D printer (30µm voxel size, Fig. 3). Recently fabricated microcontainers exhibit a size of 300µm (2). While it is possible to 3D print microcontainers with a size of 500µm (Fig. 4), the printing of the microstructures in the optimized designs is limited by the resolution. Therefore, the size of the microcontainers is scaled up by a factor of 8,3. The resolution limitation for printing a 300µm microcontainer is illustrated in Fig.5.

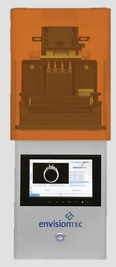

Fig.3 EnvisionTec Micro Plus Hi-Res DLP µSLA 3D printer.

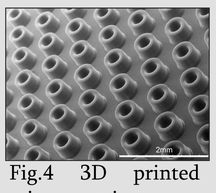

Fig.4 3D printed microcontainers.

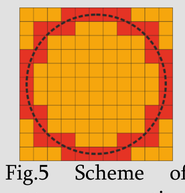

Fig.5 Scheme of pattern generation in DLP 3D printing.

Characterization

In order to evaluate the performance of the alternative designs, the adhesiveness of the microcontainers to porcine intestinal tissue was tested using two different methods:

1. Small 3D printed chips with the respective surface topology of the optimized designs were assayed for mucoadhesion with a Texture Analyzer using a contact time of 60 seconds and a contact force of 10g.
2. 3D printed single microcontainers were used to determine their flow retention profiles - both, facing up and facing down - using a custom made setup for the ex-vivo intestinal flow retention assay, first described by Rao and Buri (6).

Fig.6 Mucoadhesion test rig on a texture analyzer.

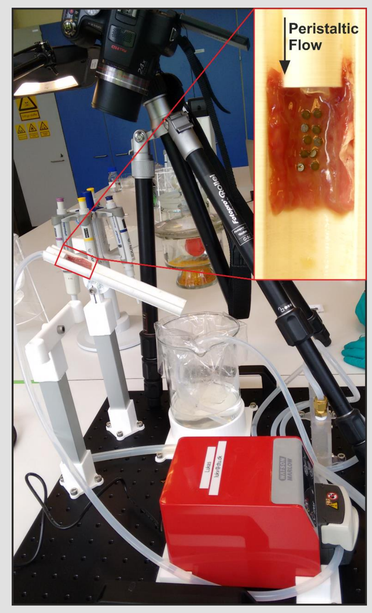

Fig.7 Setup of ex-vivo intestinal flow retention assay.

RESULTS

Scanning electron microscopy of 3D printed samples

Scanning electron microscopy (SEM) analysis was conducted with all 3D printed samples in order to determine the quality of the print outcome. The fabricated chips intended for the Texture Analyzer analysis (Fig. 8) exhibit well defined structures and an overall good print quality.

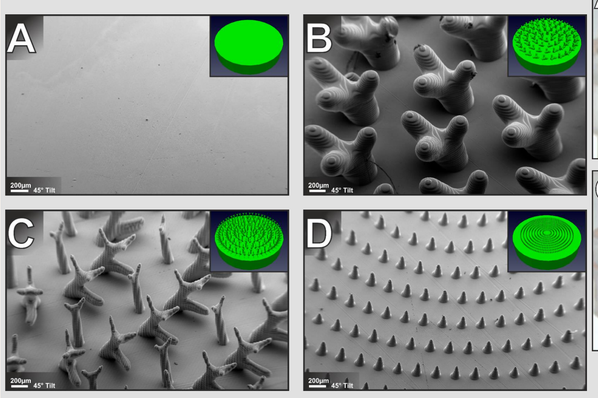

Fig. 8 SEM images of samples used for Texture Analyzer experiments. (A) Control. (B) TO1-big. (C) TO2-complex. (D) Manual design with micropillars. The corresponding designs for 3D printing are shown in the upper right corner of the SEM images.

The single microcontainer samples fabricated for the evaluation of bioadhesion using an ex-vivo intestinal flow retention assay (Fig. 9) reveal very good print outcomes. The structures also prove to be unharmed by the detachment from the printer.

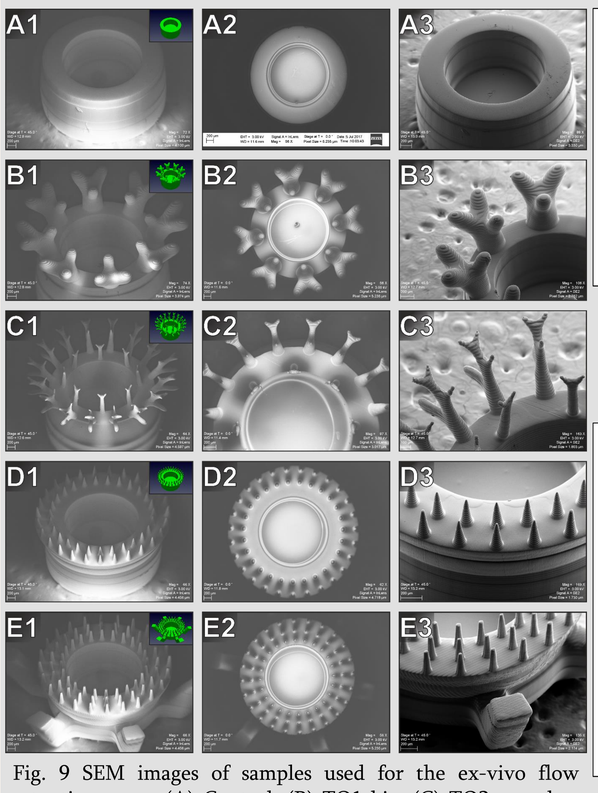

Fig. 9 SEM images of samples used for the ex-vivo flow retention assay. (A) Control. (B) TO1-big. (C) TO2-complex. (D) Manual design with overhang and micropillars. (E) Bio-inspired phage-like design.

Determination of mucoadhesion using a Texture Analyzer

Photos shot at the same time point during detachment of each sample from the tissue visualize the mucoadhesion of the samples (Fig. 10). The samples TO1-big and TO2-complex showed the highest adhesion.

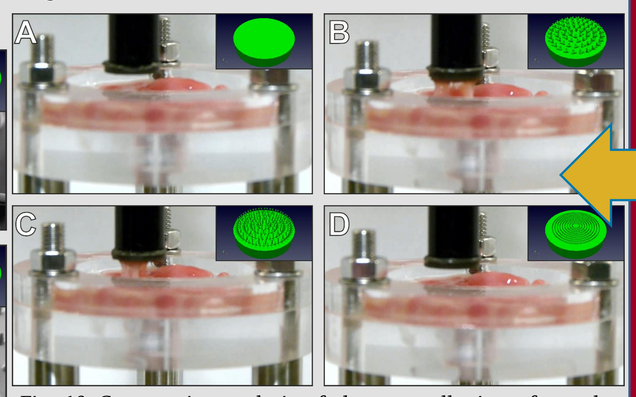

Fig. 10 Comparative analysis of the mucoadhesion of samples with different surface topologies using a Texture analyzer. All the images were taken 1 minute after detachment from the intestinal tissue was initiated. The time of contact was 1 minute and the contact force was 10g. (A) Control. (B) TO1-big. (C) TO2-complex. (D) Manual design with simple micropillars.

Ex-vivo intestinal flow retention assay

The area under the curve of the retention profiles (Fig. 11) were compared and statistically analyzed (Fig. 12). All optimized designs were found to be more adhesive than the control.

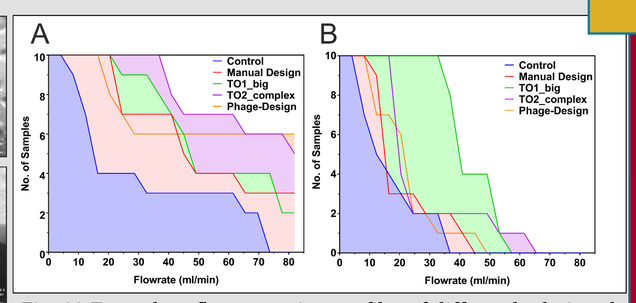

Fig. 11 Exemplary flow retention profiles of differently designed 3D printed samples. The experiment always started with 10 microcontainers. The samples were flushed with each flow rate for 2 min. (A) Microcontainers were facing down. (B) Microcontainers were facing up.

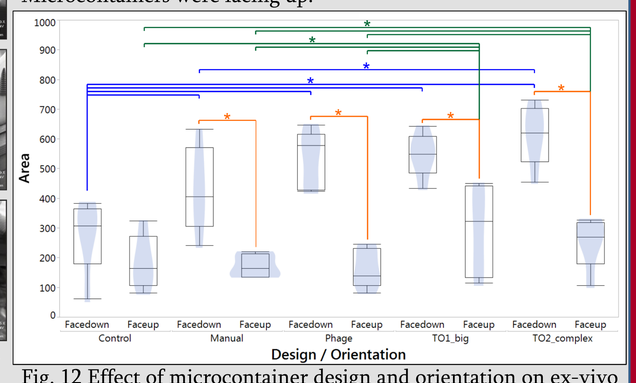

Fig. 12 Effect of microcontainer design and orientation on ex-vivo intestinal flow retention time. The experiments were repeated on 5 different pieces of porcine intestinal tissue. (* = significant with $\alpha = 0{,}05$)

CONCLUSION & OUTLOOK

- ✓ Microcontainers were successfully fabricated using 3D printing technology
- ✓ Designs created with a topology optimization approach reveal higher mucoadhesion than other designs in Texture Analyzer studies
- ✓ All alternative designs reveal significantly higher retention in an ex-vivo flow retention assay with respect to the control (commonly used design)
- ✓ All optimized designs have significantly higher retention in an ex-vivo flow retention assay when they are oriented with their textured side facing the intestinal tissue

Future studies will include the analysis of smaller 3D printed microcontainers with alternative designs, the loading with a model drug and oral bioavailability studies in rats. Furthermore, a fluidic flowcell with integrated imaging technology will be developed to analyze the flow behavior of differently shaped microcontainers in order to give an indication about preferred adhesion-orientations.

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